Antiviral Therapy of Chronic Hepatitis B and Prevention of Hepatocellular Carcinoma

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It has been well recognized that hepatitis B virus (HBV) plays a key role in the multifactorial and multistage process of hepatocarcinogenesis. The precise mechanisms by which HBV infection leads to HCC are not clearly known. Clinical and epidemiologic studies have shown that HBV replication is the key to disease activity and subsequent disease progression, including development of hepatocellular carcinoma (HCC), in patients with chronic HBV infection. In addition, the risk of HCC increases with the increasing stage of underlying liver disease, reported to be 800/100,000 per person-years in chronic hepatitis B and up to 6,000 per 100,000 person-years in cirrhosis patients. Elimination or, at least, suppression of HBV is the key to resolve hepatitis and thereby prevent or reduce cirrhosis development and further disease progression and HCC development. Among the currently available anti-HBV drugs, the most extensive experience with the use of these agents in controlling disease progression has been gained with conventional interferon-α (IFN-α) and lamivudine. Although the short-term response rate to IFN-α therapy is only 30-40%, overall data show that IFN-α has long-term beneficial effect in reducing cirrhosis, its complications and HCC development, especially in HBeAg-positive patients and those demonstrating a sustained response. Therapy with direct antiviral agent may also reduce worsening of fibrosis, reverse advanced fibrosis, and reduce cirrhosis development. Maintenance lamivudine therapy may prevent further disease progression in patients with advanced fibrosis or cirrhosis. In the woodchuck hepatitis model, sustained suppression of viral replication by direct antiviral agent may significantly reduce or delay HCC development. Maintenance lamivudine therapy in patients with chronic hepatitis and patients with advanced fibrosis or cirrhosis also showed that maintained HBV suppression, even with persistent seropositivity for hepatitis B e antigen, significantly reduced HCC development. The main problem is the emergence of drug resistance and resumption of HBV replication, which may negate the therapeutic benefits. This problem can now be overcome by timely use of adefovir or entecavir. However, the efficacy of current antiviral therapy is still far from satisfactory. The development of safe and affordable agents and the establishment of management strategies capable of producing a high rate of sustained HBV suppression without inducing drug resistance would be the ultimate goal in the management of chronic HBV infection to prevent or reduce cirrhosis and HCC development.

References

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